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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DEC 12 1986

TO: Mr. R. Taylor, PM # 25
Herbicides/Fungicides Branch
Registration Division TS-767C

THRU: R. Jaeger, Section Head
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

FROM: D. Ritter, Toxicologist
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

Subject: EPA # 1471/147 and 101 - Tebuthiuron, Company response to reject letter of 11/18/85. 21 Day Rabbit Dermal Toxicity Assay.

Registrant: Elanco, Greenfield, IN.

Caswell #: 366AA.

Elanco responds to certain findings cited in the 10-30-85 TOX review of a 21 Day Dermal study (# B01484, dated March, 1985, Acc. # 258052, Ray Landolt). The study was classified as CORE Supplementary because the single treatment level did not constitute a NOEL. The findings, the Company responses and our evaluations are as follows:

TOX review finding:

A NOEL is less than 1000 mg/kg based on the following considerations:

1. Decreased body weight gain and food consumption were observed for one animal.

Company response:

1. Such effects are common among animals during the first week of treatment. The animal subsequently gained weight. No histopathological effects or obvious clinical signs were present. The effects were isolated, and were not related to treatment.

Our Evaluation:

1. We agree with the Sponsor. That the effects occured in only one animal out of five treated supports his contention that they could not be firmly attributed to exposure to tebuthiuron.

TOX review finding:

2a. Significant increases in treated male blood glucose levels.

2b. Decrease in bilirubin and alkaline phosphatase values in treated males.

Company response:

2a. Blood glucose levels in the Sponsor's rabbit colony show a wide variation depending on the time feed was last ingested and on the individual animals'-response to handling. The treated male animal blood glucose values were only 10.9% higher than the controls' values at termination but were 10.5% less than the initial values and were well within historical normal limits.

2b. Values for treated male bilirubin and alkaline phosphatase were also within normal limits for these parameters. Since there were no supporting histopathological alterations the findings are not of toxicological significance.

Our Evaluation:

2a. We agree with the Sponsor as to glucose. This parameter is highly variable even in normal subjects and can be influenced by such things as physical stress(1). Moreover, the fairly small increase (10.9%) over control values can reasonably be considered to be within normal limits.

2b. The reduced values reported for bilirubin and alkaline phosphatase in treated animals in this study were not statistically significantly different when compared to the controls.

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(1) Tietz, N. W. Chemical Guide to Laboratory Tests. Saunders. 1983. pp. 230-232.

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TOX review finding:

3. Decreased female relative adrenal weights were reported.

Company Response:

3. The decreases were slight and not statistically different from those of the controls.

Our Evaluation:

3. The decreases were not statistically significant; hence the apparent effect is not toxicologically meaningful.

TOX review finding:

4. Increased absolute and relative spleen weights were reported for the treated females and males.

Company Response:

4. These values for the treated animals were within the normal range of variability in the Sponsor's colony. Moreover, the differences were not statistically significant.

Our Evaluation:

4. We agree with the Sponsor. The differences in relative and absolute spleen weights in the treated females were small and were not statistically significant when analysed using Student's "t" test.

TOX review finding:

5. One treated female showed a congested liver.

Company Response:

5. The finding was not supported by histopathological or clinical chemistry/hematology findings. The occurence in one female is considered to be isolated and not related to exposure to tebuthiuron.

Our Evaluation:

5. We agree with the Sponsor. An isolated occurence of a finding cannot of itself be considered a treatment-related effect.

Overall Conclusions:

We agree with all the Sponsor's responses. The effects noted were in no instance indicative of demonstrated toxicological response.

Accordingly, we conclude that the study should be reclassified as CORE Guideline, and that it therefore fulfills the requirement for the 21 day Dermal Toxicity assay under 40 CFR §158.135 (82-2).